

APT 34 AMDT

WHAT IS CLAIMED IS:

1. An antifibrillrogenic agent for inhibiting amyloidosis and/or for cytoprotection, which comprises a peptide of Formula I, an isomer thereof, a retro or a retro-inverso isomer thereof or a peptidomimetic thereof:

Xaa₁-Xaa₂-Xaa₃-Xaa₄

I

wherein,

Xaa₁ selected from the group consisting of Lys, Xaa,- Lys-;

Xaa₃ is selected from the group consisting of Lys, His-Gln-, His-His-Gln-, Val-His-His-Gln-, Glu-Val-His-His-Gln-, Asp-Asp-Asp-, Gln-;

Xaa₂ is any amino acid;

Xaa₃ is Val;

Xaa₄ is selected from the group consisting of Phe, Phe-NH₂, Phe-Phe, Phe-Phe-Ala, Phe-Phe-Ala-NH₂, Phe-Phe-Ala-Gln, Phe-Phe-Ala-Gln-NH₂;

wherein said peptide has at least one [D] amino acid residue,

with the proviso that Lys-Lys-Leu-Val-Phe-Phe-Ala is an all-[D] peptide.

2. The antifibrillrogenic agent of claim 1, wherein Xaa₂ is a hydrophobic amino acid residue.

3. The antifibrillrogenic agent of claim 1, wherein the peptide of formula I has at least two [D] amino acid residues.

4. The antifibrillrogenic agent of claim 1, wherein the peptide of formula I has at least three [D] amino acid residues.

NOT 3A ANDT

5. The antifibrillrogenic agent of claim 1, wherein the peptide of formula I has one [L] amino acid residue.

6. The antifibrillrogenic agent of claim 1, wherein the peptide of formula I is an all-[D] isomer peptide.

7. The antifibrillrogenic agent of claim 1, 2, 3, 4, 5, or 6, wherein said peptide of Formula I is selected from the group consisting of:

Lys-Ile-Val-Phe-Phe-Ala (SEQ ID NO:1);
 Lys-Lys-Leu-Val-Phe-Phe-Ala (SEQ ID NO:2);
 Lys-Leu-Val-Phe-Phe-Ala (SEQ ID NO:3);
 Lys-Phe-Val-Phe-Phe-Ala (SEQ ID NO:4);
 Ala-Phe-Phe-Val-Leu-Lys (SEQ ID NO:5);
 Lys-Leu-Val-Phe (SEQ ID NO:6);
 Lys-Ala-Val-Phe-Phe-Ala (SEQ ID NO:7);
 Lys-Leu-Val-Phe-Phe (SEQ ID NO:8);
 Lys-Val-Val-Phe-Phe-Ala (SEQ ID NO:9);
 Lys-Ile-Val-Phe-Phe-Ala-NH₂ (SEQ ID NO:10);
 Lys-Leu-Val-Phe-Phe-Ala-NH₂ (SEQ ID NO:11);
 Lys-Phe-Val-Phe-Phe-Ala-NH₂ (SEQ ID NO:12);
 Ala-Phe-Phe-Val-Leu-Lys-NH₂ (SEQ ID NO:13);
 Lys-Leu-Val-Phe-NH₂ (SEQ ID NO:14);
 Lys-Ala-Val-Phe-Phe-Ala-NH₂ (SEQ ID NO:15);
 Lys-Leu-Val-Phe-Phe-NH₂ (SEQ ID NO:16);
 Lys-Val-Val-Phe-Phe-Ala-NH₂ (SEQ ID NO:17);
 Lys-Leu-Val-Phe-Phe-Ala-Gln (SEQ ID NO:18);
 Lys-Leu-Val-Phe-Phe-Ala-Gln-NH₂ (SEQ ID NO:19);
 His-His-Gln-Lys-Leu-Val-Phe-Phe-Ala-NH₂ (SEQ ID NO:20);
 His-His-Gln-Lys (SEQ ID NO:23);
 and
 Gln-Lys-Leu-Val-Phe-Phe-NH₂ (SEQ ID NO:24).

Sub
A2

34 AMDT
Sub
A2

8. The antifibrillogenic agent of claim 1, wherein the peptide of formula I is a peptide as set forth in SEQ ID NO:2 or SEQ ID NO:3.

9. A labeled conjugate for *in vivo* imaging of amyloid deposits, which comprises a conjugate of formula II:

A-B-C

II

wherein A is an amyloid plaque-targeting moiety selected from the group consisting of a peptide of Formula I as defined in claim 1, an isomer thereof, a retro or a retro-inverso isomer thereof and a peptidomimetic thereof, wherein B is a linker portion allowing attachment of the amyloid plaque-targeting moiety to C; and wherein C is a label that allows for *in vivo* imaging.

10. The labeled conjugate of claim 9, wherein Xaa, in Formula I is a hydrophobic amino acid residue.

11. The labeled conjugate of claim 9, wherein the peptide of formula I has at least two [D] amino acid residues.

12. The labeled conjugate of claim 9, wherein the peptide of formula I has at least three [D] amino acid residues.

13. The labeled conjugate of claim 9, wherein the peptide of formula I has one [L] amino acid residue.

14. The labeled conjugate of claim 9, wherein the peptide of formula I is an all-[D] isomer peptide.

15. The labeled conjugate of claim 9, 10, 11, 12, 13 or 14, wherein said peptide of Formula I is selected from the group consisting of:

Lys-Ile-Val-Phe-Phe-Ala (SEQ ID NO:1);
 Lys-Lys-Leu-Val-Phe-Phe-Ala (SEQ ID NO:2);
 Lys-Leu-Val-Phe-Phe-Ala (SEQ ID NO:3);
 Lys-Phe-Val-Phe-Phe-Ala (SEQ ID NO:4);
 Ala-Phe-Phe-Val-Leu-Lys (SEQ ID NO:5);
 Lys-Leu-Val-Phe (SEQ ID NO:6);
 Lys-Ala-Val-Phe-Phe-Ala (SEQ ID NO:7);
 Lys-Leu-Val-Phe-Phe (SEQ ID NO:8);
 Lys-Val-Val-Phe-Phe-Ala (SEQ ID NO:9);
 Lys-Ile-Val-Phe-Phe-Ala-NH₂ (SEQ ID NO:10);
 Lys-Leu-Val-Phe-Phe-Ala-NH₂ (SEQ ID NO:11);
 Lys-Phe-Val-Phe-Phe-Ala-NH₂ (SEQ ID NO:12);
 Ala-Phe-Phe-Val-Leu-Lys-NH₂ (SEQ ID NO:13);
 Lys-Leu-Val-Phe-NH₂ (SEQ ID NO:14);
 Lys-Ala-Val-Phe-Phe-Ala-NH₂ (SEQ ID NO:15);
 Lys-Leu-Val-Phe-Phe-NH₂ (SEQ ID NO:16);
 Lys-Val-Val-Phe-Phe-Ala-NH₂ (SEQ ID NO:17);
 Lys-Leu-Val-Phe-Phe-Ala-Gln (SEQ ID NO:18);
 Lys-Leu-Val-Phe-Phe-Ala-Gln-NH₂ (SEQ ID NO:19);
 His-His-Gln-Lys-Leu-Val-Phe-Phe-Ala-NH₂ (SEQ ID NO:20);
 His-His-Gln-Lys (SEQ ID NO:23);
 and
 Gln-Lys-Leu-Val-Phe-Phe-NH₂ (SEQ ID NO:24).

16. The labeled conjugate of claim 15, wherein B is selected from the group consisting of Glucose and Phe.

17. The labeled conjugate of claim 15, wherein C is ^{99m}Tc.

18. A method for the treatment of amyloidosis disorders in a patient, which comprises administering

SA AMDT

to said patient a therapeutically effective amount of a peptide of Formula I as defined in claim 1, 2, 3, 4, 5, 6, 7 or 8.

19. A method for the treatment of amyloidosis disorders in a patient, which comprises administering to said patient a therapeutically effective amount of an antifibrillogenic agent as defined in claim 1, 2, 3, 4, 5, 6, 7 or 8.

Sub
A4

20. A composition for the treatment of amyloidosis disorders in a patient, which comprises a therapeutically effective amount of a peptide of Formula I as defined in claim 1, 2, 3, 4, 5, 6, 7 or 8 in association with a pharmaceutically acceptable carrier.

21. A composition for the treatment of amyloidosis disorders in a patient, which comprises a therapeutically effective amount of an antifibrillogenic agent as defined in claim 1, 2, 3, 4, 5, 6, 7 or 8 in association with a pharmaceutically acceptable carrier.

22. A composition for in vivo imaging of amyloid deposits, which comprises a therapeutically effective amount of a labeled conjugate as defined in claim 9, 10, 11, 12, 13, 14, 15, 16 or 17 in association with a pharmaceutically acceptable carrier.

23. Use of a peptide of Formula I as defined in claim 1, 2, 3, 4, 5, 6, 7 or 8 for inhibiting amyloidosis and/or for cytoprotection.

34 AMDT

24. Use of an antifibrillrogenic agent as defined in claim 1, 2, 3, 4, 5, 6, 7 or 8 for inhibiting amyloidosis and/or for cytoprotection.
25. Use of a labeled conjugate as defined in claim 10, 11, 12, 13, 14, 15, 16 or 17 for in vivo imaging of amyloid deposits.
26. Use of a peptide of Formula I as defined in claim 1, 2, 3, 4, 5, 6, 7 or 8 for the manufacture of a medicament for inhibiting amyloidosis and/or for cytoprotection.
27. Use of an antifibrillrogenic agent as defined in claim 1, 2, 3, 4, 5, 6, 7 or 8 for the manufacture of a medicament for inhibiting amyloidosis and/or for cytoprotection.
28. Use of a labeled conjugate as defined in claim 10, 11, 12, 13, 14, 15, 16 or 17 for the manufacture of a medicament for in vivo imaging of amyloid deposits.
29. A peptide, an isomer thereof, a retro or a retro-inverso isomer thereof or a peptidomimetic thereof, for use in inhibiting amyloidosis and/or for cytoprotection, said peptide having a sequence taken from the β -sheet region of an amyloid protein selected from the group consisting of IAPP and protease resistant prion protein.
30. Use of a peptide as defined in claim 29 for inhibiting amyloidosis and/or for cytoprotection.

NET 34. AMDT

31. Use of a peptide as defined in claim 29 for the manufacture of a medicament for inhibiting amyloidosis and/or for cytoprotection.

Sub
A5

32. A composition for inhibiting amyloidosis and/or for cytoprotection, which comprises a therapeutically effective amount of a peptide as defined in claim 31, 30 or 31 in association with a pharmaceutically acceptable carrier.

Sub
A6

33. Use of a labeled peptide as defined in claim 29 for the manufacture of a medicament for in vivo imaging of amyloid deposits.

34. A process for the preparation of cells suitable for transplantation into a mammal, which cells are capable of forming amyloid deposits, said process comprising contacting the cells in vitro with the peptide of Formula I as defined in claim 1 or with the antifibrillogenic compound as defined in claim 1, 2, 3, 4, 5, 6, 7 or 8 for inhibiting amyloid deposit formation.

35. Process according to claim 34, wherein said peptide of Formula I or said antifibrillogenic compound causes breakdown of amyloid deposits, the deposits having been formed by said cells prior to said contact.

36. Process according to claim 34 or 35, in which the cells are cultured in the presence of the peptide of Formula I or the antifibrillogenic compound.

Add
A7